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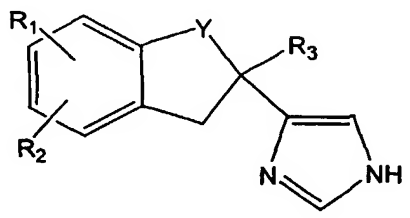
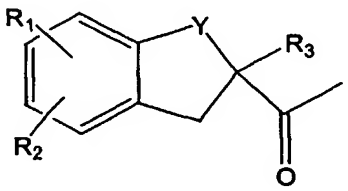
(54) Title: PROCESS FOR PREPARING SUBSTITUTED IMIDAZOLE DERIVATIVES AND INTERMEDIATES USED IN THE PROCESS



(I)



(II)

(57) Abstract: The invention relates to a process for preparing substituted imidazole derivatives of formula (I) and acid addition salts thereof (I) in which formula Y is $-CH_2-$ or -CO-, R_1 is H, halo or hydroxy, R_2 is H or halo and R_3 is H or lower alkyl, starting from a compound of formula (II) wherein Y, R_1, R_2 and R_3 are as defined above. The invention also relates to intermediates and their preparation.

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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

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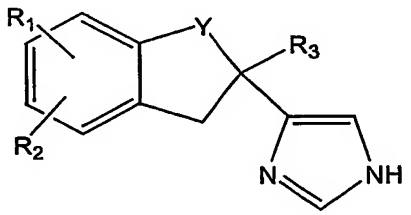
PROCESS FOR PREPARING SUBSTITUTED IMIDAZOLE DERIVATIVES AND INTERMEDIATES USED IN THE PROCESS

FIELD OF THE INVENTION

The present invention relates to a new process for preparing substituted imidazole derivatives of formula (I) and acid addition salts thereof,



(I)

in which formula Y is $-CH_2-$ or -CO-, R_1 is H, halogen or hydroxy, R_2 is H or halogen and R_3 is H or lower alkyl.

The invention also relates to intermediates used in the process and to their preparation.

BACKGROUND OF THE INVENTION

The compounds of the above-mentioned formula (I) are highly selective and long-acting antagonists of α_2-adrenoceptors and they have a good peroral bioavailability. The compounds are especially valuable in the treatment of cognitive disorders. Compounds of formula (I) have been described in patent publication EP 0 618 906 B1. Specific examples of such compounds are 4-(2-ethyl-5-fluoroindan-2-yl)-1H-imidazole and 4-(5-fluoroindan-2-yl)-1H-imidazole.

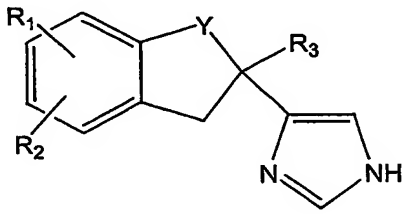
The above-mentioned publication EP 0 618 906 B1 also discloses methods of preparing compounds of formula (I). Said methods relate to various ways of modifying the substituents in the benzene moiety of the indan ring system. There is no disclosure of a total synthesis, which would lead to the desired compounds in good yield.

Publication EP 0 310 745 B1 discloses a process for preparing compounds of formula (I), wherein the last step of the process comprises the use of formamide for the formation of the imidazole ring. The use of formamide, however, requires severe reaction conditions, which should be avoided in connection with industrial production in large scale.

Although the individual steps of the process according to the present invention are known as such (see e.g. EP 0 146 228 B1), it has now surprisingly been found that compounds of formula (I) can be prepared, also in large scale, in very good yields by using the synthesis route described below.

SUMMARY OF THE INVENTION

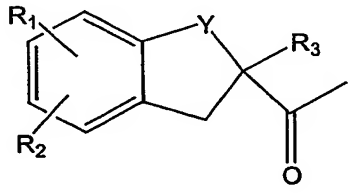
The present invention relates to a process for preparing substituted imidazole derivatives of formula (I) and acid addition salts thereof



(I)

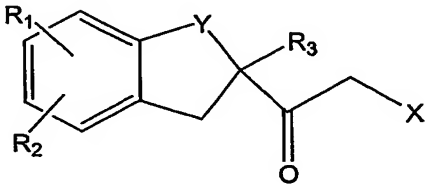
in which formula Y is $-CH_2-$ or $-CO-$, R_1 is H, halogen or hydroxy, R_2 is H or halogen and R_3 is H or lower alkyl, comprising the steps of

a) halogenating a compound of formula (II)



(II)

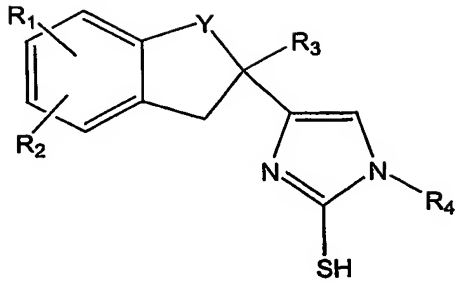
wherein Y, R_1, R_2 and R_3 are as defined above, to obtain a compound of formula (III)



(III)

wherein Y, R_1, R_2 and R_3 are as defined above and X is halogen,

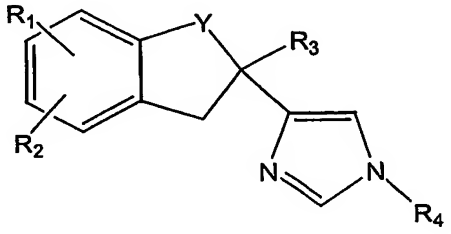
b) reacting the compound of formula (III) thus obtained with an amine of formula R_4NH_2, wherein R_4 is an easily removable leaving group, and an alkali metal thiocyanate, to obtain a compound of formula (IV)



(IV)

wherein Y, R_1, R_2, R_3 and R_4 are as defined above,

c) removing the mercapto group from the compound of formula (IV) to obtain a compound of formula (V)



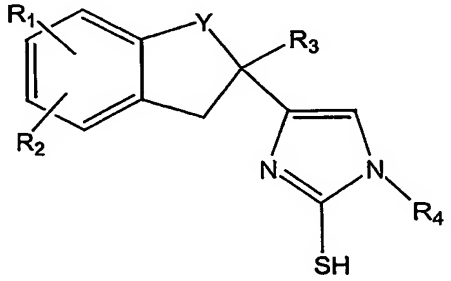
(V)

wherein Y, R_1, R_2, R_3 and R_4 are as defined above,

d) removing the group R_4 from the compound of formula (V) to obtain a compound of formula (I), and, if desired,

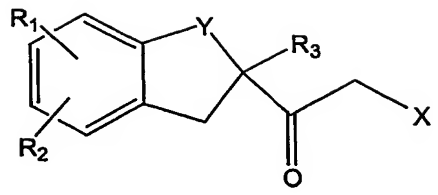
e) converting the resulting compound of formula (I) into an acid addition salt thereof.

Further the invention relates to a process for preparing a compound of formula (IV)



(IV)

wherein Y is $-CH_2-$ or -CO-, R_1 is H, halogen or hydroxy, R_2 is H or halogen and R_3 is H or lower alkyl, comprising reacting a compound of formula (III)



(III)

wherein Y, R_1, R_2 and R_3 are as defined above and X is halogen, with an amine of formula R_4NH_2, wherein R_4 is an easily removable leaving group, and an alkali metal thiocyanate.

The invention also relates to intermediate compound (IV) wherein Y, R_1, R_2, R_3 and R_4 are as defined above.

DETAILED DESCRIPTION OF THE INVENTION

In this context, the term *an acid addition salt* refers to an addition salt of any pharmaceutically acceptable acid, preferably hydrochloric or hydrobromic acid.

In this context, the term *halogen* refers to F, Cl, Br and I. Regarding R_1 and/or R_2 it preferably refers to F and/or Cl, and most preferably to F. Regarding X it preferably refers to Cl and Br, and most preferably to Br.

In this context, the term *lower alkyl* refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms and most preferably 1 or 2 carbon atoms.

In this context the term *aralkyl* refers to substituted or unsubstituted groups *-alkylene-aryl*. *Alkylene* refers to a diradical of a branched or unbranched saturated hydrocarbon chain, preferably having from 1 to 10 carbon atoms and more preferably having 1 to 6 carbon atoms and *aryl* refers to an unsaturated aromatic carbocyclic group of from 6 to 20 carbon atoms having a single ring (e.g. phenyl) or multiple condensed (fused) rings (e.g. naphthyl or anthryl).

In this context the term *easily removable leaving group* refers to any group that a person skilled in the art would know to be easily removable. Preferred *easily removable leaving groups* would be aralkyls, e.g. benzyl.

According to the present invention a compound of formula (II) is, in step a), halogenated with a halogenating agent to obtain a compound of formula (III), where X is a halogen, e.g. Br, Cl or I. A preferred halogenating

agent is Br_2. The reaction is suitably carried out in a solvent, such as an alcohol, e.g. methanol, at room temperature or below. A suitable temperature is –8 °C to +25 °C, preferably –8 °C to –5 °C.

In step b) the compound of formula (III) obtained in step a) is reacted with an amine of formula R_4NH_2 where R_4 is a easily removable leaving group, and an alkali metal thiocyanate to obtain a mercapto compound of formula (IV). The reaction is suitably carried out in a solvent, such as as an alcohol, e.g. ethanol or butanol, at an elevated temperature, preferably at reflux temperature. The amine for the reaction may be one where R_4 is aralkyl, preferably benzyl. A preferred alkali metal thiocyanat is potassium thiocyanate.

In step c) the mercapto group is removed from the compound of formula (IV) obtained in step c) to obtain a compound of formula (V). The reaction is suitably carried out in the presence of a catalyst, e.g Raney-Nickel, at a temperature of 40 °C to 90 °C, preferably 40 °C to 60 °C.

In step d) the group R_4 can be removed from the compound of formula (V) obtained in step c) by treating the compound of formula (V) with ammonium formate in the presence of a catalyst, such as Pd/C. Alternatively a catalyst, such as Raney-Nickel, may be used, or R_4 may be removed by hydrogenation in the presence of Pd/C.

The resulting compound of formula (I) may be converted into acid addition salts using methods known per se. Preferred acid addition salts are HCl and HBr.

Preferred compounds of formulae (I) to (V) are those where Y is CH_2, R_1 is F, R_2 is H and R_3 is ethyl.

The process according to the present invention makes it possible to prepare compounds of formula (I) in good yield and in a simple way, e.g. by using lower reaction temperatures, that also are suitable for large-scale production. The known methods result in poor yields and require severe reaction conditions, e.g. high temperatures, which makes large-scale production difficult. For instance, compared to the process using formamide (EP 0 310 745 B1), the process of the present invention using lower temperatures does not create separation or isolation problems relating to great amounts of various impurities that are typically formed in the known formamide process

The following examples illustrate the invention, but are not intended to restrict the scope of the invention.

Example 1

2-bromo-1-(2-ethyl-5-fluoro-indan-2-yl)-ethanone

3,8 g of 2-acetyl-2-ethyl-5-fluoroindan and 35 ml of methanol were placed into a round-bottomed flask equipped with a thermometer, a mechanical stirrer and a dropping funnel. The reaction mixture was cooled in a cooling bath while stirring to a temperature between –5 °C and –8 °C and 0,7 ml of a Br_2-solution in a small amount of methanol was added dropwise. The cooling bath was removed and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was cooled to a temperature between –5 °C and –8 °C and an additional 0,175 ml of Br_2-solution in a small amount of methanol was added dropwise. The cooling bath was removed and the reaction mixture was stirred at room temperature for an additional 1 to 2 hours. After chromatographic purification using methylene chloride as an eluent 2,51 g of 2-bromo-1-(2-ethyl-5-fluoro-indan-2-yl)-ethanone was obtained as a liquid (yield 69 %).

1H NMR (200 MHz, CDCl3, ppm): 0.85 (3H, t, J 7.6 Hz, CH2CH3), 1.82 (2H, q, J 7.5 Hz, CH2CH3), 2.83-2.93 (2 H, dd, the indan ring H2-1 or H2-3), 3.32-3.46 (2 H, dd, the indan ring H2-1 or H2-3), 4.11 (2H, s, CH2-Br), 6.79-7.10 (3H, m, Ar-H)
HPLC-MS: 285-286-287 (68, M+, Br-isotopes), 205 (72), 187 (100).
UV (Lambda-max): 208 nm (Abs. 1.01020 AU), 271 nm (Abs. 0.27428 AU), 277 nm (Abs. 0.27026 AU).

Example 2

1-benzyl-5-(2-ethyl-5-fluoro-indan-2-yl)-imidazole-2-thiol

1,62 g of 2-bromo-1-(2-ethyl-5-fluoro-indan-2-yl)-ethanone was dissolved in 25 ml of ethanol in a glass round-bottomed flask equipped with a mechanical stirrer, a thermometer and a dropping funnel. The reaction mixture was heated to reflux temperature while stirring. 0.366 g of benzylamine dissolved in 5 ml ethanol was added slowly in a drop-wise fashion to the solution. After the addition of benzylamine the mixture was refluxed for one hour. 0,330 g of potassium thiocyanate was added portionwise during 30

minutes and the reaction mixture was refluxed for 2 hours. The reaction mixture was evaporated to dryness before 150 ml ethyl acetate was added and the solution was washed with water. The organic phase was dried over Na_2SO_4, filtered and evaporated providing 1,13 g of 1-benzyl-5-(2-ethyl-5-fluoro-indan-2-yl)-imidazole-2-thiol (yield 31 %). The analytical sample was purified using TLC-plates. The purity was measured by HPLC: 62 %. Normally the crude product was used in the following step.

1H NMR (200 MHz, $CDCl_3$, ppm): 0.75 (t, $CH_2C\underline{H}_3$), 1.80 (q, $C\underline{H}_2CH_3$), 2.81-3.30 (m, the indan ring H_2-1 and H_2-3), 5.18 (s, N-$C\underline{H}_2$-Ar), 6.24 (s, -S$\underline{H}$), 6.77-7.09 (m, Ar-H, im-H), 7.23-7.36 (m, Ar-$\underline{H}$-CH_2-N).
HPLC-MS: 353 (100, M+), 221 (29), 187 (12).

Example 3

1-benzyl-5-(2-ethyl-5-fluoro-indan-2-yl)-imidazole

7,5 ml of Raney-Nickel prepared according to Vogel, Practical Organic Chemistry, 5th Edition, 1999, Longman, U.K. p. 450-451, was mixed with 20 ml of ethanol under nitrogen atmosphere in a round-bottomed flask equipped with a thermometer and a stirring bar. 500 mg of 1-benzyl-5-(2-ethyl-5-fluoro-indan-2-yl)-imidazole-2-thiol was dissolved in 10 ml of ethanol and added to the mixture. The reaction mixture was stirred at 40 °C for about 10 hours and then the temperature was raised to 60 °C for 2 hours followed by cooling to room temperature. The mixture was filtered and the filter (Celite™) was washed with ethanol. The ethanol solution was evaporated to dryness to obtain 151 mg of a crude product. After chromatographic purification using methylene chloride, methylene chloride:methanol (10:1) and methylene chloride:methanol (1:1) as eluents 1-benzyl-5-(2-ethyl-5-fluoro-indan-2-yl)-imidazole was obtained. The purity was measured by HPLC: 83 %.

1H NMR (200 MHz, MeOD, ppm): 0.70 (3H, t, $CH_2C\underline{H}_3$), 1.82 (2H, q, $C\underline{H}_2CH_3$), 2.90-3.01 (2 H, dd, the indan ring H_2-1 or H_2-3), 3.13-3.25 (2 H, dd, the indan ring H_2-1 or H_2-3), 5.10 (2H, s, N-$C\underline{H}_2$-Ar), 6.72-6.87 (3H, m, Ar-H, im-H), 7.05-7.18 (3H, m, Ar-H, Ar-$\underline{H}$-CH_2-N), 7.29-7.32 (3H, m, Ar-$\underline{H}$-CH_2-N), 7.56 (1H, s, im-$\underline{H}$).
HPLC-MS: 321 (100, M+).

Example 4

4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole

53 mg of 1-benzyl-5-(2-ethyl-5-fluoro-indan-2-yl)-imidazole, 20 mg of Pd/C, 51 mg of ammonium formate and 2 ml of ethanol were added under nitrigen atmosphere into a round-bottomed flask equipped with a thermometer and a stirring bar. The reaction mixture was stirred at reflux temperature for 6 hours. The mixture was filtered and the filter (Celite™) was washed with ethanol. The reaction mixture was placed back into a round-bottomed flask and an additional 20 mg of Pd/C and 51 mg of ammonium formate were added under nitrogen atmosphere. The mixture was heated to reflux temperature and refluxed for 2 hours. Then the mixture was cooled to room temperature and filtered. The filter (Celite™) was washed with ethanol and after evaporation to dryness, whereby 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole was obtained. The analytical sample was purified using TLC-plates. The purity was measured by HPLC: 60 %. Normally the crude product was used in the following step.

1H NMR (200 MHz, MeOD, ppm): 0.76 (t, $CH_2C\underline{H_3}$), 1.29 (q, $C\underline{H_2}CH_3$), 2.98-3.22 (m, the indan ring H_2-1 and H_2-3), 6.78-6.94 (m, Ar-H, im-H), 7.09-7.19 (m, Ar-H, im-H).
HPLC-MS: 231 (100, M+).

Example 5

4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole

10 ml of the crude product obtained in Example 3 was placed in a round-bottomed flask equipped with a thermometer and a stirring bar. 1,5 ml of Raney-Nickel in ethanol (Raney-Nickel prepared according to Vogel, Practical Organic Chemistry, 5th Edition, 1999, Longman, U.K. p. 450-451), was added under nitrogen atmosphere. The reaction mixture was stirred at reflux temperature for about 14 hours. After filtration and evaporation crude 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole was obtained.

HPLC-MS: 231 (100, M+).

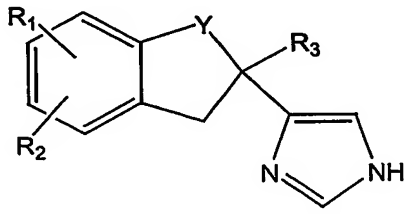
Example 6

4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole-hydrochloride

A HCl/methanol reagent was prepared by bubbling HCl-gas through methanol. 100 mg of 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole was dissolved in 2 ml methanol in a round-bottomed flask. 2 ml of HCl/methanol reagent (3 M) was added slowly to the solution while stirring. During the addition the internal temperature of the mixture was kept below 29 °C by cooling. The resulting mixture was evaporated at a temperature between 35 °C and 40 °C to viscous colourless oil whereupon it was dissolved in 2 ml of acetone at the same temperature. The solution was cooled to a temperature between 10 °C and 15 °C at which temperature the mixture started to crystallize. The crystalline material was filtered, washed with cooled acetone and dried in a vacuum oven at 35 °C overnight. A second crop was isolated from the mother liquid followed by cooling, filtering and drying as described above. The yield of 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole-hydrochloride was altogether 87% of the theoretical, m.p. 171 – 173 °C.

Claims

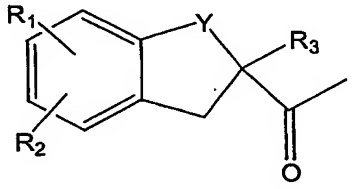
1. A process for preparing substituted imidazole derivatives of formula (I) and acid addition salts thereof



(I)

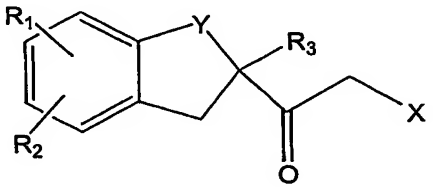
in which formula Y is $-CH_2-$ or -CO-, R_1 is H, halogen or hydroxy, R_2 is H or halogen and R_3 is H or lower alkyl, comprising the steps of

a) halogenating a compound of formula (II)



(II)

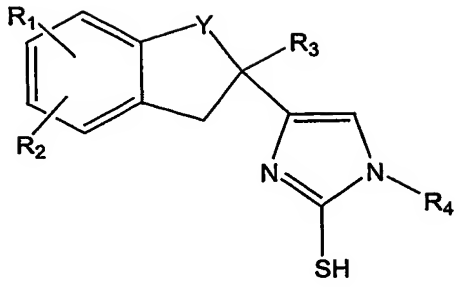
wherein Y, R_1, R_2 and R_3 are as defined above, to obtain a compound of formula (III)



(III)

wherein Y, R_1, R_2 and R_3 are as defined above and X is halogen,

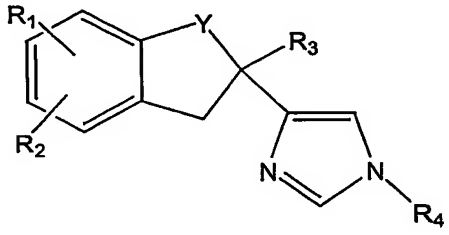
b) reacting the compound of formula (III) thus obtained with an amine of formula R_4NH_2, wherein R_4 is an easily removable leaving group, and an alkali metal thiocyanate, to obtain a compound of formula (IV)



(IV)

wherein Y, R_1, R_2, R_3 and R_4 are as defined above,

c) removing the mercapto group from the compound of formula (IV) to obtain a compound of formula (V)



(V)

wherein Y, R_1, R_2, R_3 and R_4 are as defined above,

d) removing the group R_4 from the compound of formula (V) to obtain a compound of formula (I), and, if desired,

e) converting the resulting compound of formula (I) into an acid addition salt thereof.

2. A process according to claim 1 wherein step a) is carried by reacting a compound of formula (II) with Br_2 in methanol at a temperature of - 8 to +25 °C.

3. A process according to claim 1 or 2 wherein step b) is carried out by reacting a compound of formula (III) with benzylamine and potassium thiocyanate.

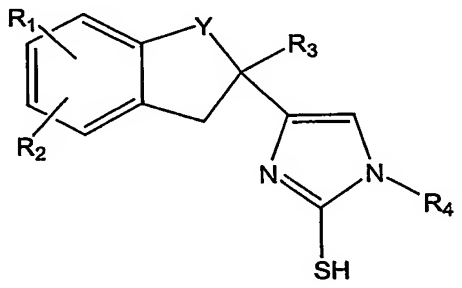
4. A process according to any of claims 1 to 3 wherein step c) is carried out in the presence of Raney-Nickel at a temperature of 40 °C to 90 °C.

5. A process according to any of claims 1 to 4 wherein step d) is carried out by using ammonium formate in the presence of Pd/C.

6. A process according to any of claims 1 to 4 wherein step d) is carried out by hydrogenation in the presence of Pd/C.

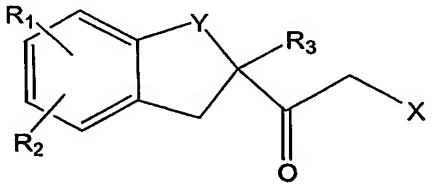
7. A process according to any of claims 1 to 6 wherein Y is $-CH_2-$, R_1 is F, R_2 is H and R_3 is ethyl.

8. A process for preparing a compound of formula (IV)



(IV)

wherein Y is $-CH_2-$ or -CO-, R_1 is H, halogen or hydroxy, R_2 is H or halogen and R_3 is H or lower alkyl, comprising reacting a compound of formula (III)



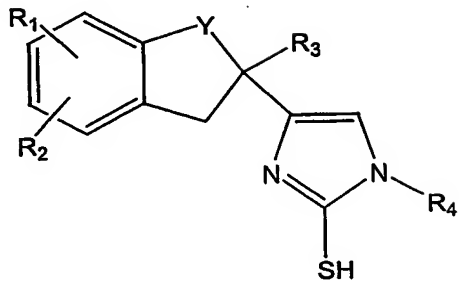
(III)

wherein Y, R_1, R_2 and R_3 are as defined above and X is halogen, with an amine of formula R_4NH_2, wherein R_4 is an easily removable leaving group, and an alkali metal thiocyanate.

9. A process according to claim 8 comprising reacting a compound of formula (III) with benzylamine and potassium thiocyanate.

10. A process according to claim 8 or 9 wherein Y is $-CH_2-$, R_1 is F, R_2 is H and R_3 is ethyl.

11. A compound of formula (IV)



(IV)

wherein Y is $-CH_2-$ or -CO-, R_1 is halogen or hydroxy, R_2 is H or halogen, R_3 is H or lower alkyl and R_4 is an easily removable leaving group.

12. A compound according to claim 11 wherein Y is $-CH_2-$, R_1 is F, R_2 is H, R_3 is ethyl and R_4 is benzyl.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/FI2004/000004

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D233/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03/099795 A (ALLERGAN INC) 4 December 2003 (2003-12-04) page 114, compound 156 Table 1, compounds 143,145,148,149,151,153,155,163,164	11
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A	EP 0 146 228 A (FARMOS OY) 26 June 1985 (1985-06-26) cited in the application page 3, line 26 - line 50	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
28 May 2004	21/06/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Diederen, J

INTERNATIONAL SEARCH REPORT

International Application No
PCT/FI2004/000004

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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